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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/622,055	CERNERUD ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *herewith* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the invention of Group I, in the reply filed on 14 November 2005 to the Requirement for Restriction mailed 8 August 2005, is acknowledged.

Applicants' counsel indicates in the reply, at page 2, that the election is made without traverse to the extent that it was understood that the pharmaceutical composition claim and method of use claims will be rejoined upon allowance of the compound claims. Indeed, claims drawn to a pharmaceutical composition comprising allowable Group I compounds and methods of treatment comprising administering allowable Group I compounds (Group II in the Requirement for Restriction), and also the methods of making allowable Group I compounds (Group IV) will be rejoined upon allowance Group I claims. At such time, the Requirement for Restriction between Groups I, II and IV would be withdrawn. As stated in the Requirement for Restriction (bottom of page 4), the subject matter of claim 20 will not be deemed commensurate in scope with Group I for the purposes of rejoinder, because of the recitation of a radiolabelled compound of formula (I), for which no antecedent basis is present in instant claim one.

Elected Group I is not in condition for allowance, as is detailed in the following pages, thus, the inventions of Groups II and IV are not eligible for rejoinder at this time.

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of the compounds following formula (I), pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers and *N*-oxides thereof, does not reasonably provide enablement for prodrug forms thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Wands factors provide a guide for determining the scope of enablement provided by a given disclosure:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claim 1, from which claims 2-13 and 28 depend, is limited to chemical entities of formula (I) having the structure depicted in the claim, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of chemical entities having the formula (I) is that they be pharmacologically inactive.

Prodrugs come in myriad forms, and are not limited to only carbamate esters and amides, which are commonly cited as examples, and suggested as the preferred type of prodrug on page 14 of the instant specification. A prodrug may be an carboxylate ester, a Mannich base (imine), an acyclic precursor to a cyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug, to name a few.

So, the scope of all possible types of prodrugs is quite broad. A prodrug does not necessarily depend on the identity of the pharmacologically active agent formed upon its metabolism for patentability. A prodrug is not necessarily even structurally related to the compound of which it is a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a chemical entity having the formula (I) are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. When a compound, on the other hand, is designed specifically at the outset to function as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, that is he must know to what extent and how the compound will be metabolized. The metabolism of xenobiotics compounds in animals is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew exactly how a given new compound will be metabolized and to what extent, and also knew which structural modifications would yield an inactive compound that upon metabolism, would be converted into an active drug, prodrug structures could be predicted in advance. The reality is that these considerations must be empirically derived. Prodrug structures cannot be predicted.

(F) The specification does not provide any direction specific to the preparation of a prodrug of a formula (I) compound. No metabolic studies of the compounds have been completed by applicants and no structure-activity rules are outlined in the specification – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not mention any type of prodrug other than "such as a carbamate or an amide" on page 14, at line 26.

(G) No working examples, out of the 76 preparative examples, of a prodrug is provided in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of chemical entities having the formula (I), a complete structure activity analysis of each one of the chemical entities embraced by formula (I) would have to be completed. This analysis would involve thousands of individual compounds. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active chemical entities of formula (I) *in vivo*

identified. This research would potentially be inconclusive and could take years. Additionally, one of ordinary skill in the art would necessarily have to undertake an effort to make totally new compounds not bearing any structural similarity to the chemical entities having the formula (I), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the chemical entities having formula (I) would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways in different species, this effort would have to be duplicated in each species for which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making prodrugs of chemical entities having the formula (I), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so. Thus, the full scope of instant claim 1 is not enabled by the disclosure.

****

Claims 1-13 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "and prodrug forms thereof," present as a limitation in claim 1, renders that claim indefinite in scope. As such, any claim dependent therefrom, specifically claims 2-13 and 28, are also not of clear and well-defined scope. The claims are drawn to chemical compounds which chemical compounds are prodrugs of the specified molecular structure of formula (I). Although some fairly obvious "prodrug" candidates could be identified by one of ordinary skill (*e.g.*, carbamate esters or amides, as taught at page 14 of the specification), the *full scope* of *all* molecular structures which would and could yield a compound according to the instant claims upon metabolism in some (unidentified) animal is not readily apparent from a reading of the claims in light of the specification.

Simply because one of ordinary skill in the art understands what *function* a prodrug serves or what the word "prodrug" means is not enough to apprise him of what *molecular structures* lie within the scope of claims 1-13 and 28 and what structures lie without. The specification does not provide any teachings specifically applicable to the compounds disclosed therein which will render the claimed prodrugs. No metabolism studies of formula (I) compounds are disclosed in the instant specification either.

A rejection of the term "prodrugs" under the first paragraph of this statute precedes this indefiniteness rejection of the same term. Applicants' attention is directed to section "A" – the breadth of the claims – for an explanation of what is

actually contemplated by "prodrug." It is more than simply esters or amides of the compounds which have the specified molecular structures in the instant claims. This rejection is not being made in view of the breadth of the term "prodrug" but rather because of the complexity that the term adds to the claim. One of ordinary skill in the art, to be apprised of what is actually covered by the claims, would have to be aware of all chemical compounds which would or could be metabolized into a compound having the specified molecular structures in any animal species, which is practically impossible.

Claim 13, in addition to being indefinite for depending from claim 1, which is indefinite in scope, is further indefinite because the phrase "and solvates" lacks antecedent basis in claim 1. Claim 1 only specifies hydrates of formula (I) compounds, while the term "solvates" is broader in scope than "hydrates." Amendment of claim 1 to recite "solvates" instead of "hydrates" will necessitate the setting forth of a rejection under 35 U.S.C. 112, first paragraph, for lack of enablement of the full scope of all solvates of formula (I) compounds.

Title of the Application

The specification is objected to under 37 C.F.R. 1.72(a). The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is commended to applicants that the current title "New Compounds" be replaced with a new title, "$5HT_{2A}$ Receptor Antagonists."

Allowable Subject Matter

Subject matter of claims 1-13 and 28 is free from the prior art. If the rejections under 35 U.S.C. 112, stated in the preceding, are overcome, claims 1-13 and 28 would be in allowable form, and claims of Groups II and IV, as were set forth in the Requirement for Restriction mailed 8 August 2005, would be rejoined therewith.

The closest prior art with respect to claims 1-13 and 28 is represented in the references cited in the Information Disclosure Statement filed 26 September 2003 by applicants. 1-(2-pyrazinyl)-pyrazines wherein the pyrazinyl ring is further substituted with a carbonyl ("oxo") at the 3-position *and* an alkylenyl-aryl (or heteroaryl) group at the 4-position are novel and unobvious in view of the closest prior art. Lumma et al, *Journal of Medicinal Chemistry*, vol. 24(1), pages 93-101 (1981) discloses a compound particularly similar to a compound according to instant claim 1 on page 97 in Table II. These 2-(1-piperazinyl)-3-(4*H*)-quinoxalinones however, *do not* have a substituent on the quinoxaline-one nitrogen atom adjacent to the carbonyl as required by the instant claims.

The following comments are presented as a courtesy to applicants:

Upon rejoinder of the claims of Group II, rejection of claims 15-18 under the first paragraph of 35 U.S.C. 112 will be necessary, should the changes described in the attached Interview Summary not be adopted. As demonstrated by the following cited references, the state of the art at the time the instantly claimed invention was made (in 2002), with respect to the therapeutic application of $5HT_{2A}$ receptor antagonists, was not such that treatment of or prophylaxis of all

diseases within the scope of claims 15-18 was practicable by one of ordinary skill in the art.

de Angelis, "5-HT2A antagonists in psychiatric disorders" Current Opinion in Investigational Drugs, vol. 3(1), pages 106-112 (2002).

and,

Kihara et al, "AT-1015, a Novel Serotonin (5-HT)2 Receptor Antagonist, Blocks Vascular and Platelet 5-HT2A Receptors and Prevents the Laurate-Induced Peripheral Vascular Lesion in Rats" Journal of Cardiovascular Pharmacology, vol. 35(4), pp. 523-530 (2000)

De Angelis teaches that $5HT_{2A}$ receptor antagonists have therapeutic utility for the treatment of schizophrenia, depression, tardive dyskinesia (also known as “extrapyramidal symptoms”), anorexia nervosa, obsessive-compulsive disorder, drug dependence and alcohol dependence.

Kihara et al deals with the cardiovascular therapeutic utility of $5HT_{2A}$ receptor antagonists, which are considerable. The $5HT_{2A}$ receptor antagonist studied by Kihara et al had demonstrable activity blocking the vasoconstriction induced by 5HT, platelet aggregation inhibitory effects. At page 11 of the Kihara et al reference, the authors conclude that a $5HT_{2A}$ receptor antagonist would have utility in the treatment of peripheral vascular disease. Thus, the treatment of the peripheral vascular diseases/conditions recited in instant claim 16 is deemed enabled by the disclosure.

In short, treatment of the following conditions and diseases is not enabled by the disclosure: fibromyalgia, thrombotic illness including stroke, memory disorders, mood disorders, autism, depressive disorders *including depression*

disorders with coexisting diabetes (though treatment of depressive disorders is enabled by the disclosure), sexual function disorders, sleep disorders, pain, Parkinson's disease, glaucoma including normal tension glaucoma, urinary incontinence including urinary incontinence with coexisting diabetes and "diabetic complications." Prophylaxis of no condition or disease is enabled by the disclosure because prophylaxis requires complete elimination of the disease or condition.

The examiner notes that in the instant specification, at pages 2-4, several patents and publications are cited, ostensibly as providing enabling support for the methods according to claims 15-19. Treatment of only one of the conditions or diseases the treatment of which is identified in the preceding sentences as not being enabled by the disclosure is actually *claimed* in a United States patent cited in the instant specification. A method for the treatment of fibromyalgia *per se* is not claimed in US 4,877,798, rather, claim 1 of that patent specifies the treatment of the symptomatology of fibromyalgia, which is generally defined in the specification (col. 1, lines 8-15) of that patent as including widespread musculoskeletal pains, aching, fatigue, and sleep disturbances. The underlying disease, fibromyalgia, is not treated by the method of claim 1 of US patent 4,877,798.

Treatment of glaucoma with a $5HT_{2A}$ receptor antagonist, though claimed in US 5,106,855 (to McLees) was not recognized as a viable treatment option in 2002, when the instant invention was made. As evidence of this fact, the examiner directs applicants' attention to the following two references:

Camras et al, "Efficacy and Adverse Effects of Medications Used in the Treatment of Glaucoma" Drugs & Aging, vol. 15(5), pages 377-388 (November 1999).

and,

Phelan Peter "Reappraising First-Line Treatment in Glaucoma Management" Hospital Medicine, vol. 63(9), pages 540-545 (September 2002).

Both are reviews on current pharmacological management of glaucoma, one written in 2002, the year the instantly claimed invention was made, and one written in 1999, three years before the invention was made. Neither mentions anything about $5HT_{2A}$ antagonists. It is fair to say therefore that a physician of ordinary skill in the art of treating glaucomas, an ophthalmologist, would not have known how to treat glaucoma with a compound having the pharmacological activity possessed by those according to the instant claims ($5HT_{2A}$ antagonism), at the time the invention was made.

In the interest of compact prosecution, applicants should look to the amendments suggested in the attached Interview Summary.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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